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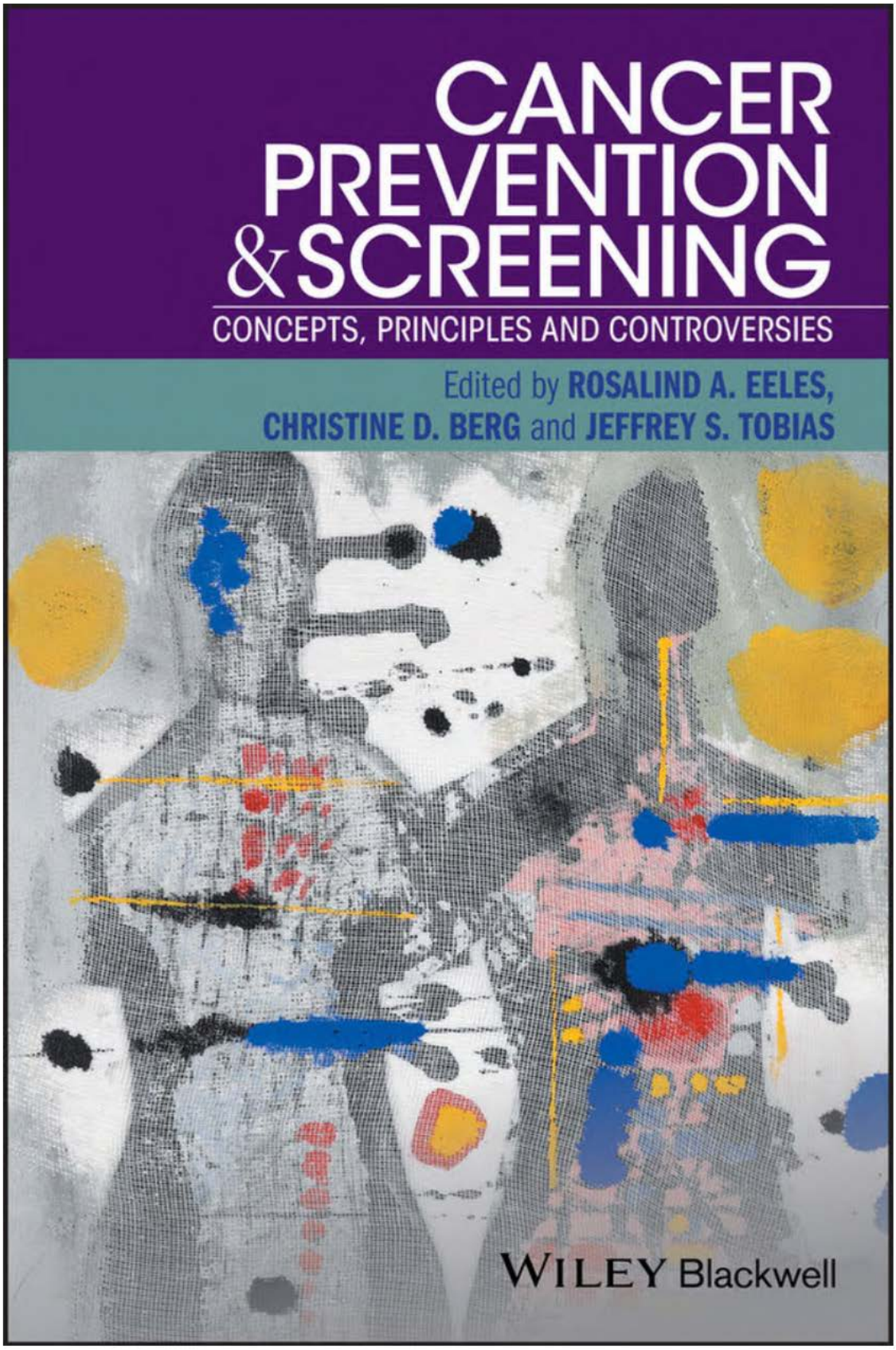
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Cancer prevention and screening

Concepts, principles and controversies

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CHAPTER 23

Ovarian cancer prevention and screening

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SUMMARY BOX

- Major efforts have been made to identify risk factors for ovarian cancer and to build risk-prediction models that combine epidemiological, genetic, and epigenetic factors in order to improve risk stratification.
- Future preventive strategies such as the oral contraceptive pill, aspirin, and opportunistic salpingectomy and screening strategies are likely to be based on individual risk estimates using such models.
- There is good evidence that multimodal screening using serum CA125 interpreted using ROCA with TVS as a second-line test has encouraging performance characteristics.
- Screening for ovarian cancer in the general population is currently not recommended. However, results of the UK Collaborative Trial of Ovarian Cancer Screening suggest a mortality reduction associated with multimodal screening of around 20%. If this is confirmed on further follow-up of two to three years, it is likely to have an impact on future recommendations.
- Women at high risk are advised to undergo risk-reducing salpingo-oophorectomy. For those opting not to undergo surgery, in the UK screening is currently not available on the NHS, but is advocated at six-monthly intervals in the USA.
- A drive to develop a new generation of screening tests based on tumour DNA and novel specimens such as cervical samples is under way.

Ovarian cancer (OC) is the most fatal of all gynaecological malignancies and accounts for around 4% of all cancers diagnosed in women. Worldwide, there are 239 000 new cases of OC each year, of whom 7270 are in the UK [1]. While 10-year age-standardized survival has increased in England from 18% during 1971–1972 to 35% during 2010–2011, two-thirds of women die within 10 years of diagnosis [2]. Most of the improvement in survival has occurred in early-stage

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disease, highlighting the importance of diagnosing early-stage/low-volume disease. This has led to ongoing efforts to explore risk stratification, prevention, and screening, which form the focus of this chapter. Given that epithelial OC is a heterogeneous disease, it is unlikely that one strategy will be effective for all histological subtypes (high-grade serous, endometrioid, clear-cell, low-grade serous, mucinous). In addition, recent evidence on precursor lesions such as serous tubal intraepithelial carcinoma (STIC) in a proportion of high-grade serous cancers suggests the need to explore novel solutions beyond routine tests such as serum CA125 and transvaginal ultrasound.

Lifetime risk of ovarian cancer

The average woman's lifetime risk of ovarian cancer is 1.9% [3], but there are women at substantially higher (40–60%) and lower risk. It is increasingly possible to stratify women based on their genetic and epidemiological risk factors [3].

Risk factors

Age

There is a strong correlation with age, with 83% of cases occurring in women over 50 years. The incidence rates rise sharply from an age-standardized rate of 8.9 per 100 000 in women aged 35–39 to a peak of 69.2 per 100 000 in those aged 80–84 [4].

Family history

The strongest risk factor is a family history of breast and multiple ovarian cancers [5] or the Lynch syndrome cancers (bowel, endometrium, stomach, kidney, ovary, skin in multiple relatives) [6, 7]. Women with a single first-degree relative with ovarian cancer may have up to a threefold increased risk [8]. Genetic predisposition could be due to alterations in the following:

High-penetrance genes

These include mutations in the *BRCA1* and *BRCA2* genes, with average cumulative risk of epithelial OC by the age of 70 of 40–60% (*BRCA1*) and 11–27% (*BRCA2*) mutation carriers [9]. Emerging evidence suggests that *BRCA* germline mutations are present in 14% of women with invasive nonmucinous epithelial ovarian cancer, and 22% of those with high-grade serous epithelial ovarian cancer [10]. This has led to efforts to extend genetic testing for *BRCA* genes to all women with nonmucinous epithelial OC at the point of diagnosis. *BRCA* mutations occur at a rate of 1 in 300 to 1 in 500 in most populations [11], but significantly increase to 1 in 40 in the Ashkenazi Jewish population [11]. In the latter group, there is growing evidence that identification of individuals through family history alone misses over half of those with mutations in *BRCA1/2*

[12–15]. Using systematic testing in such populations with a high prevalence of mutations has recently been shown to be acceptable and cost-effective [16], and suggests that 3.6% of OCs could be prevented if population testing for *BRCA1/2* was available [17].

In Lynch syndrome, the lifetime risk of OC is lower and related to the specific mutations (approximately 2–15%) [18] in at least five different DNA mismatch repair genes [19], with the highest risk in *MLH1* and *MSH2* carriers.

Moderate-penetrance genes

Several susceptibility genes that confer more moderate penetrance risks of OC, such as *RAD51C* [20, 21], *RAD51D* [22], and *BRIP1* [23], have been described and may account for the excess familial risk in these women. The magnitude of risk associated with these alleles seems to be similar to those associated with *BRCA2* mutations. Most recent data suggest that *RAD51C* mutations are associated with a 6.8-fold increased risk of OC, *RAD51D* with a 10-fold increased risk [24], while *BRIP1* deleterious mutations carry a relative risk of OC of 11, increasing to 14 for high-grade serous OCs [25]. Some of these moderate-penetrance genes have been included in commercially available gene-testing panels for ovarian (OvaNEXT™) and breast and ovarian cancer (GeneDX™), without sufficient evidence to support their clinical significance. These multigene panels are constrained by the accuracy of prediction/definition of risk and clinical use [26].

Low-penetrance inherited genetic variants

Through the efforts of the Ovarian Cancer Association Consortium, a worldwide initiative currently consisting of 76 groups, 37 common low-risk (low-penetrance) loci have been identified [27–37], with the strongest association with the serous subtype. Subtype-specific single-nucleotide polymorphisms (SNPs) for the other histological subtypes have also been identified [38]. Individually, these loci confer an increase in relative risk of 1.2–1.4. Despite possible risk stratification based on these SNPs, the clinical implications are still not clear. Some of these loci have been shown to alter OC risk in mutation carriers, with four of these being associated with OC risk in *BRCA2* carriers and two in *BRCA1* carriers [39]. Despite the huge effort in identifying new disease susceptibility loci, the known genetic factors identified so far only account for less than half of the heritable risk for OC [8]. This indicates that other susceptibility alleles exist and that only a fraction of the risk variants have been identified. A major consortia-wide effort (Collaborative Oncological Gene-environment Study, COGS) has contributed to identifying some of the 37 loci included above [29]. However, risk stratification based on the emerging genetic factors will need to be carefully thought through [40].

Epidemiological factors

Established protective factors for OC include oral contraceptive pill (OCP) use, pregnancy, breast-feeding, and tubal ligation, thought to exert their effect through reduction of the number of ovulatory cycles in a woman, while nulliparity and infertility are associated with increased risk (Table 23.1). Of particular interest is

Table 23.1 Risk factors for ovarian cancer (OC).

Risk Factor	OR/RR	95% CI	Author	Year
Oral contraceptive pill (OCP)	0.73	0.66–0.81	Havrilesky et al. [85]	2013
OCP duration (>120 months)	0.43	0.37–0.51		
OCP age at first use (<20)	0.63	0.45–0.89		
OCP type (combined)	0.68	0.55–0.83	Faber et al. [86]	2013
OCP type (combined and progestin only)	0.5	0.28–0.87		
OCP type (progestin only)	0.97	0.45–2.14		
Tubal ligation	0.82	0.68–0.97	Rice et al. [41]	2013
Tubal ligation* (adjusted for age, OCP use, parity)	0.33	0.16–0.64	Hankinson et al. [87]	1993
Tubal ligation	0.87	0.78–0.98	Madsen et al. [44]	2015
Primary invasive epithelial ovarian cancer				
Serous	0.92	0.79–1.08		
Endometrioid	0.66	0.47–0.93		
Mucinous	1.25	0.94–1.67		
Clear cell	1.03	0.65–1.62		
Other	0.6	0.43–0.83		
Borderline	1.03	0.89–1.21		
Salpingectomy			Madsen et al. [44]	2015
Unilateral	0.9	0.72–1.12		
Bilateral	0.58	0.36–0.95		
Hysterectomy with unilateral oophorectomy	0.65	0.45–0.94	Rice et al. [41]	2013
Simple hysterectomy	1.09	0.83–1.42		
Age ≥45	0.64	0.40-1.02		
Underwent procedure within 10 years of questionnaire	0.65	0.38–1.13		
Overall (regardless of year of OC diagnosis)	0.81	0.72–0.92	Jordan et al. [43]	2013
Median year of OC diagnosis pre-2000	0.7	0.65–0.76		
Median year of OC diagnosis post-2000	1.18	1.06–1.31		

Continued

Table 23.1 Continued

Parity			Fortner et al. [88]	2015
Full-term pregnancy	0.73	0.58–0.92		
Borderline	1.12	0.59–2.13		
Type I invasive epithelial ovarian cancer	0.47	0.33–0.69		
Type II invasive epithelial ovarian cancer	0.81	0.61–1.06		
Parous	0.71	0.61–0.85	Yang et al. [89]	2012
Serous	0.83	0.65–1.06		
Endometrioid	0.49	0.30–0.80		
Mucinous	0.54	0.25–1.14		
Clear cell	0.28	0.13–0.62		
Other	0.76	0.56–1.04		
Breastfeeding			Fortner et al. [88]	2015
Borderline	1.02	0.54–1.93		
Type I	0.67	0.41–1.08		
Type II	0.85	0.64–1.13		
Infertility treatment			Jensen et al. [90]	2009
Gonadotrophins	0.83	0.50–1.37		
Clomifene	1.14	0.79–1.64		
Human chorionic gonadotrophin	0.89	0.62–1.29		
Gonadotrophin-releasing hormone	0.8	0.42–1.51		
Endometriosis			Pearce et al. [54]	2012
Low-grade serous	2.11	1.39–3.20		
Endometrioid	2.04	1.67–2.48		
Clear cell	3.05	2.43–3.84		
Obesity			Olsen et al. [46]	2013
Serous	0.98	0.94–1.02		
Low-grade serous	1.13	1.03–1.25		
Endometrioid	1.17	1.11–1.23		
Mucinous	1.19	1.06–1.32		
Borderline (serous)	1.24	1.18–1.30		

Continued

Table 23.1 Continued

Risk Factor	OR/RR	95% CI	Author	Year
Cigarette smoking			Faber et al. [47]	2013
Current				
Mucinous	1.13	1.03–1.65		
Borderline (mucinous)	1.83	1.39–2.41		
Former				
Borderline (serous)	1.3	1.12–1.50		
Hormone replacement therapy (HRT)	1.33	1.16–1.53	Yang et al. [89]	2012
Current users			Collaborative Group on Epidemiological Studies of Ovarian Cancer [48]	2015
<5 years duration	1.43	1.31–1.56		
≥5 years duration	1.41	1.34–1.49		
Past users (<5 years since last use)				
<5 years duration	1.17	0.97–1.38		
≥5 years duration	1.29	1.11–1.49		
Past users (≥5 years since last use)				
<5 years duration	0.94	0.88–1.02		
≥5 years duration	1.1	1.01–1.20		
Estradiol-only therapy (5 years or more)			Koskela-Niska et al. [49]	2013
Serous	1.45	1.20–1.75		
Mucinous	0.35	0.19–0.67		
Estradiol–progestin therapy (5 years or more)				
Sequential	1.35	1.20–1.63		
Sequential (endometrioid)	1.88	1.24–2.86		
Ever use			Fortner et al. [88]	2015
Borderline	0.62	0.33–1.03		
Type I	0.92	0.56–1.51		
Type II	1.12	0.85–1.48		

Continued

Table 23.1 Continued

Aspirin			Baandrup et al. [91]	2015
Low dose	0.94	0.85–1.05		
Low dose – long-term use (over 5 years)	0.77	0.55–1.08		
150 mg	0.82	0.68–0.99		
Statins	0.98	0.87–1.10	Baandrup et al. [53]	2015
Mucinous	0.63	0.39–1.00		

CI, confidence interval; OR, odds ratio; RR, risk ratio.

the reduction of OC risk associated with the OCP, with over 10 years' use associated with a 50% risk reduction. A stronger protective effect of the OCP has been found in women at high risk due to *BRCA1/2* mutations, and again the effect is proportional to duration of use.

Hysterectomy had for many years been thought to reduce the risk of OC. More recently, no evidence of an association between simple hysterectomy and ovarian cancer has been reported [41, 42] with an increased risk of OC with hysterectomy reported in women being diagnosed with OC after 2000 [43]. Although this temporal change is difficult to explain, it may possibly be due to a decrease in overall hysterectomy rates, move towards a vaginal rather than abdominal approach, decline in bilateral salpingo-oophorectomy performed at the same time, and increase in the age of those undergoing the procedure.

There is now observational population-based data that bilateral salpingectomy alone may be associated with a 42% (odds ratio [OR] 0.58; 95% confidence interval [CI] 0.36–0.95) decrease in ovarian cancer risk [44].

Lifestyle factors

A lot of work has been done to clarify the risk reduction of various lifestyle approaches, such as alcohol [45], obesity [46], cigarette smoking [47], and talc use. Some of these are subtype specific, such as endometriosis, cigarette smoking, and obesity, while others are 'general risk factors'. Use of talc in the genital area has consistently been shown to increase the risk of OC and therefore it is not recommended.

Drugs

Hormone replacement therapy

Data from the observational studies show an increased risk of OC with hormone replacement therapy (HRT) use. An individual participant meta-analysis of 52 epidemiological studies reported that women who use hormone therapy for five years from around age 50 have about one extra ovarian cancer per 1000 users [48]. Estradiol-only therapy (if used for five years or more) increases the risk

of serous OC by 45%, but decreases the risk of mucinous OC by 65%, while estradiol–progestin therapy (five years or more), if used as a sequential regimen, increases the risk by 35% compared to the continuous regimen, which did not (Table 23.1) [49].

Aspirin

More recently, low-dose aspirin has been shown to be associated with a reduction of ovarian [50] and endometrial cancer [51] risk in the general population. There is emerging evidence of risk reduction of ovarian and endometrial cancers in high-risk women with Lynch syndrome as well [52].

Statins

Limited data indicate a decreased risk of ovarian cancer among those using statins. Recently, a large Danish nationwide study of 4103 cases and 58 706 controls reported a neutral association between ever using statins and OC risk (OR 0.98, 95% CI 0.87–1.10) [53].

Other risk factors

Women with endometriosis are at an increased risk of epithelial OC. An analysis of 13 ovarian cancer case-control studies from the Ovarian Cancer Association Consortium has shown that women who self-reported endometriosis were substantially more likely to develop clear-cell (OR 3.05, 95% CI 2.43–3.84), low-grade serous (OR 2.11, 95% CI 1.39–3.20), and invasive endometrioid ovarian cancers (OR 2.04, 95% CI 1.67–2.48) [54]. There was no association between endometriosis and risk of mucinous or high-grade serous invasive epithelial OC or borderline tumours of either subtype. Risk related to endometriosis was less pronounced in multiparous women compared to nulliparous, again suggesting the protective effect of parity.

Recent evidence indicates that endometriosis-associated OC shows favourable characteristics, including low-grade and early-stage disease. But it is unlikely that the presence of endometriosis affects disease progression after the onset of OC. Consequently, in those with a diagnosis of endometriosis, timely treatment may be advisable to reduce the OC risk.

Risk-prediction models

Significant efforts are under way to improve risk prediction. There are several predictive models that use family history to estimate mutation risk in *BRCA* genes and lifetime risk of OC, such as BRCAPRO, BODICEA, and Myriad II, as well as the Finnish, US National Cancer Institute, University of Pennsylvania, and Yale University models [55]. Although each model is unique based on the methods/population used, their performances in identifying women who have a high probability of carrying a *BRCA1/2* mutation have similar discrimination ability, ranging from 71% (Yale) to 83% (BRCAPRO) [56]. Such models may prove as useful tools

to assess cancer risk on a population basis in the future. Major efforts are now under way to further improve prediction using a combination of genetic and epidemiological factors. It is likely that in the future risks of a lower magnitude (<10% lifetime risk of OC) may instigate consultations between women and their gynaecologists [3].

Prevention

In the context of OC, all strategies available reduce risk but do not completely eliminate the possibility of a cancer arising in the future.

Risk-reducing surgery

Risk-reducing salpingo-oophorectomy (RRSO) reduces ovarian cancer risk in *BRCA* mutation carriers by 85% [57]. It is associated with a relatively low complication rate (3.9%; 95% CI 2.0–6.7%) [5]. RRSO is routinely recommended in high-risk women after completion of their families. While the standard recommendation is from the age of 35, it is important to individualize this, especially in women with *BRCA2* gene mutations. In Lynch syndrome women, the risk-reducing surgery includes hysterectomy. Removal of the ovaries leads to premature menopause, which is associated with increased morbidity and mortality, and hence RRSO is usually accompanied by use of HRT till the age of natural menopause [58]. Based on emerging evidence that most high-grade serous ovarian cancers originate in the fallopian tubes and involve the ovary secondarily [59], removal of the tubes alone has been put forward as an alternative risk-reducing strategy. McAlpine et al. [60] have already reported on the uptake, risk, and complications of opportunistic salpingectomy. This has been widely implemented in women undergoing pelvic surgery in Canada and endorsed by the Society of Gynecologic Oncology in the USA [61]. Gynaecologists surveyed in the UK have indicated that they would be willing to undertake bilateral salpingectomy at the time of hysterectomy (92%) or tubal ligation (65%) [62]. More recently, an approach based on bilateral salpingectomy with delayed oophorectomy in BRCA mutation carriers is being trialed in the United States [63]. Similar trial is to launch in the United Kingdom.

Aspirin

In the CAPP2 randomized controlled trial (RCT) of Lynch syndrome women, aspirin (600 mg a day for at least two years) reduced the risk of colorectal cancer (hazard ratio [HR] 0.63, 95% CI 0.35–1.13, p=0.12), with a similar effect on other noncolorectal Lynch syndrome cancers (HR 0.63, 95% CI 0.34–1.19, p=0.16) [52]. Hence it is increasingly applied (with some women using a 75 mg low-dose regime) to reduce the risk of ovarian and endometrial cancer in these women. The current trial (CaPP3) [64] due to report in 2020 is assessing the lowest dose (100, 300, and 600 mg per day) that confers such risk reduction in these women.

Oral contraceptive pill

Due to side effects, it is not currently recommended that women, especially those in their 40s, take OCP solely for OC risk reduction. That is, however, an added advantage, especially in those at high risk, who are considering using OCP for contraception or other medical indications.

Screening for ovarian cancer

Currently, there is no screening programme for ovarian cancer. In 2012, the US Preventative Task Force (USPSTF) reaffirmed its previous recommendation that screening should not be undertaken in the general population [65]. The National Institute for Health and Clinical Excellence (NICE) guidance in the UK advises that investigations should be carried out in women (especially if 50 years or over) only if reporting persistent or frequent symptoms (abdominal distension, early satiety, loss of appetite, pelvic or abdominal pain, or increased urinary urgency and/or frequency), particularly if more than 12 times per month [66]. However, recent evidence from the UK trial suggests that annual screening in the general population using a multimodal approach may be associated with a mortality benefit, which needs to be confirmed on further follow-up [67].

General population

In view of the improved survival in OC patients detected at an early stage, and the fact that a screening strategy based on CA125 and ultrasound demonstrated survival advantage in the screened women, large RCTs of OC screening were set up in the mid-1990s. The results of the ovarian arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, an RCT where 30 630 women aged 55–74 between 1993 and 2007 underwent screening using serum CA125 with a cut-off of ≥35 kU/l and transvaginal ultrasound (TVS) for four years, followed by CA125 alone for a further two years, showed no mortality benefit (mortality rate ratio 1.18, 95% CI 0.91–1.54) at a median follow-up of 12.4 years. Moreover, there was a high (15%) serious complication rate in women undergoing surgery for false-positive findings [68]. Updated data based on extended follow up at median of 14.7 years re-confirmed the lack of mortality benefit [69].

More encouraging data from the Kentucky single-arm ultrasound study of 37 293 women (a mean follow up of 5.8 years) found five-year survival rates in women with primary invasive epithelial cancer who were screened to be significantly higher (74.8% ± 6.6%) compared to unscreened nonstudy women (53.7% ± 2.3%) [70]. However, these rates are not comparable due to the 'lead-time effect' of screening and the likelihood of a significant healthy volunteer effect in those who participated in the screening study [71].

The largest RCT to date is the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), in which 202 638 women from the general population

were randomized to no intervention (control) or annual screening using either transvaginal ultrasound (USS, n=50 639) or serum CA125 interpreted using the 'Risk of Ovarian Cancer' algorithm (ROCA), with transvaginal ultrasound as a second-line test (multimodal screening, MMS, n=50 640). Screening was completed at the end of 2011. On the prevalence screen, both MMS and USS strategies had encouraging sensitivity for primary invasive epithelial ovarian/tubal cancers (iEOC; 89.5% and 75%, respectively) [72]. During incidence screening in the MMS arm, sensitivity and specificity of the multimodal strategy for iEOC was 86%, with 4.8 women undergoing surgery/detected iEOC. The ROCA assigns risk of ovarian cancer based on age and CA125 profile. Interpreting the annual serum CA125 using the ROCA detected 86.5% (134/155) of iEOC diagnosed within one year of the screen, while an approach using fixed CA125 cut-off at the last annual screen of >35, >30, or >22U/mL would have identified 41.3%, 48.4%, and 66.5%, respectively. The area under the curve for ROCA (0.915) was significantly (p=0.0027) higher than for a single threshold rule (0.869), with screening using ROCA doubling the number of screen-detected iEOCs compared to a fixed cut-off [73]. Independent validation of the UK findings of high specificity and positive predictive value of ROCA was reported from a single-arm US prospective study of 4051 low-risk postmenopausal women [74].

Mortality outcome data from UKCTOCS based on follow-up until 31 December 2014 suggests that screening using the multimodal strategy may result in a reduction in ovarian cancer mortality [67]. There was a significant stage shift of iEOC and primary peritoneal cancers in the MMS arm (36.1% Stage I/II) compared to control (23.9% Stage I/II). The reduction in ovarian and tubal cancer deaths (MMS 15%; USS 11%) over 14 years was not significant in the primary Cox analysis comparing either group to control. However, this overall estimate comprised a reduction of 8% in the first seven years of the trial and 23% in years 7–14 in the MMS group, and 2% and 21%, respectively, in the USS group. This delayed mortality effect of screening was similar to that seen in other screening trials, and was associated with a significant (p=0.023) mortality reduction in the MMS versus control comparison, using the weighted log-rank analysis adopted by the PLCO trialists. A significant (p=0.021) mortality reduction of 20% was also observed in the MMS group when the prevalent cases (women who had OC prior to the start of trial) were excluded from the analysis. The mortality reductions in the USS arm were not significant. With regard to harms, per 10 000 screens, 14 women in the MMS arm and 50 in the USS arm underwent trial surgery as a result of positive screen results and were then found to have only benign ovarian lesions or normal ovaries. The major surgical complication rate in the latter was low (3.1% MMS and 3.5% USS) and similar to those usually reported for such surgery. The initial cost-effectiveness analysis demonstrated that the MMS strategy falls within the NICE threshold [75]. Further follow up for four years is currently underway before firm conclusions on the efficacy and cost-effectiveness of screening can be reached.

High risk

Annual screening for OC is not recommended in high-risk women, as it is not effective in detecting early-stage disease [76]. A shorter screening interval of four months using serum CA125 interpreted by ROCA and transvaginal ultrasound was investigated in the UK Familial Ovarian Cancer Screening Study (UKFOCSS) Phase II. Such intensive screening will lead to women recalled for abnormal results experiencing transient cancer-specific distress, but there was no significant effect on general anxiety/depression or overall reassurance [77].

The results of Phase II demonstrate a significant stage shift in women diagnosed with invasive epithelial ovarian, tubal and peritoneal cancers within 1 year of last screen (63% Stage I-IIIA) compared with those diagnosed >1 year after screening ended (6% Stage I-IIIA; p=0.0004). Moreover, there were higher rates of zero residual disease after debulking (95% versus 72%; p=0.09) and lower rates of neoadjuvant chemotherapy (5% versus 44%; p=0.008) in those detected within a year of the last screen [78]. The performance of a similar strategy using ROCA has been evaluated prospectively in screening trials in women at high risk in the USA (Cancer Genetics Network, CGN, and Gynaecology Oncology Group, GOG) and reported similar stage shift [79].

There are currently differing views on whether screening should be offered to high-risk women. In the UK in the NHS there is no screening for OC in high-risk women, with risk management confined to RRSO and symptom awareness. However, in the USA, while the primary recommendation is risk-reducing surgery, the US National Comprehensive Cancer Network guidelines consider six-monthly screening using serum CA125 and TVS a reasonable approach for those who do not wish to undergo surgery.

Future directions

The goal is to develop a new generation of screening tests based on tumour DNA [80], in view of the recent emerging evidence that TP53 mutations could be detected in vaginal sections of 60% of patients with high-grade serous cancer, and novel specimens such as cervical samples [81]. More recently, a multi-analyte test (CancerSEEK) of eight biomarkers including CA125 and TP53 mutations exhibited a high sensitivity of 98% for ovarian cancer [82].

Symptom awareness

Symptoms for ovarian cancer, albeit nonspecific, are not 'silent', but may lead to earlier diagnosis with less tumour burden [83]. In the UK, NICE issued guidelines in 2011 stating that any women (especially those over 50) presenting to primary care with persistent abdominal distension/'bloating', feeling full and/or loss of appetite, pelvic/abdominal pain, increased urinary urgency and/or frequency, unexplained weight loss, fatigue, or changes in bowel habit should have a CA125 test followed by TVS. However, during the NHS campaign 'Be Clear on Cancer',

the high prevalence (14% of those over 45 years presenting to primary care had frequent and/or severe symptoms) of these gynaecological cancer symptoms has become evident [84]. Use of public awareness campaigns is probably best aimed at those at high risk, as otherwise the burden in increase in consultation could be unmanageable.

Conclusion

There is a significant effort under way to identify epidemiological and genetic risk factors for ovarian cancer and improve on the current risk-prediction models so that prevention and screening can be tailored to the individual. In high-risk women, RRSO following completion of the family is recommended. There is an increasing trend to recommend low-dose aspirin to women with Lynch syndrome. There is good evidence that multimodal screening using serum CA125 interpreted using ROCA with TVS as a second-line test has the best performance characteristics to date. Recent data from UKCTOCS suggest that annual multimodal screening may be associated with a mortality benefit in the general population, with estimates of mortality reduction of around 20%. Further follow-up is required to confirm the effect size and the cost-effectiveness before any general population screening is considered. Recommendations for high-risk women who decide not to undergo RRSO are controversial. Whilst 4-monthly screening using ROCA demonstrated significant stage shift, screening is currently not available on the NHS in the UK, but is recommended six-monthly in the USA. In the meantime, major efforts are in progress to explore preventive strategies such as opportunistic bilateral salpingectomy in both the low- and high-risk populations, and to develop a new generation of screening tests based on tumour DNA and novel specimens such as cervical samples.

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